



UNIVERSITÀ  
DEGLI STUDI  
FIRENZE

# FLORE

## Repository istituzionale dell'Università degli Studi di Firenze

### **Risk of complications in patients with conservatively managed ovarian tumours (IOTA5): a 2-year interim analysis of a multicentre,**

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

*Original Citation:*

Risk of complications in patients with conservatively managed ovarian tumours (IOTA5): a 2-year interim analysis of a multicentre, prospective, cohort study / Froyman, Wouter; Landolfo, Chiara; De Cock, Bavo; Wynants, Laure; Sladkevicius, Povilas; Testa, Antonia Carla; Van Holsbeke, Caroline; Domali, Ekaterini; Fruscio, Robert; Epstein, Elisabeth; dos Santos Bernardo, Maria José; Franchi, Dorella; Kudla, Marek Jerzy; Chiappa, Valentina; Alcazar, Juan Luis; Leone, Francesco Paolo Giuseppe; Buonomo, Francesca; Hochberg,

*Availability:*

This version is available at: 2158/1154726 since: 2020-05-29T15:48:03Z

*Published version:*

DOI: 10.1016/S1470-2045(18)30837-4

*Terms of use:*

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

*Publisher copyright claim:*

(Article begins on next page)

# Risk of complications in conservatively managed ovarian tumours during the first 2 years of follow-up: interim analysis of the multicentre IOTA5 prospective cohort study

Wouter Froyman<sup>1,2</sup> MD, Chiara Landolfo<sup>1,3</sup> MD, Bavo De Cock<sup>1</sup> MSc, Laure Wynants<sup>1</sup> PhD, Povilas Sladkevicius<sup>4</sup> PhD, Antonia Carla Testa<sup>5</sup> Professor, Caroline Van Holsbeke<sup>6</sup> PhD, Ekaterini Domali<sup>7</sup> PhD, Robert Fruscio<sup>8</sup> Professor, Elisabeth Epstein<sup>9</sup> PhD, Maria José dos Santos Bernardo<sup>10</sup> MD, Dorella Franchi<sup>11</sup> MD, Marek Jerzy Kudla<sup>12</sup> PhD, Valentina Chiappa<sup>13</sup> MD, Juan Luis Alcazar JL<sup>14</sup> Professor, Francesco Paolo Giuseppe Leone<sup>15</sup> MD, Francesca Buonomo<sup>16</sup> MD, Lauri Hochberg<sup>17</sup> MD, Maria Elisabetta Coccia<sup>18</sup> PhD, Stefano Guerriero<sup>19</sup> Professor, Nandita Deo<sup>20</sup> FRCOG, Ligita Jokubkiene<sup>4</sup> PhD, Jeroen Kaijser<sup>21</sup> PhD, An Coosemans<sup>2,22</sup> PhD, Ignace Vergote<sup>2,22</sup> Professor, Jan Yvan Verbakel<sup>23,24</sup> Professor, Tom Bourne<sup>1,2,3</sup> Professor, Ben Van Calster<sup>1,25</sup> Professor, Lil Valentin<sup>4\*</sup> Professor, Dirk Timmerman<sup>1,2\*</sup> Professor

\* Contributed equally

1 KU Leuven, Department of Development and Regeneration, Leuven, Belgium; 2 Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium; 3 Queen Charlotte's and Chelsea Hospital, Imperial College, London, UK; 4 Department of Obstetrics and Gynecology, Skåne University Hospital Malmö, Lund University, Sweden; 5 Department of Woman and Child Health, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore Roma, Rome, Italy; 6 Department of Obstetrics and Gynecology, Ziekenhuis Oost-Limburg, Genk, Belgium; 7 First Department of Obstetrics and Gynecology, Alexandra Hospital, Medical School, National and Kapodistrian University of Athens, Greece; 8 Clinic of Obstetrics and Gynecology, University of Milan-Bicocca, San Gerardo Hospital, Monza, Italy; 9 Department of Clinical Science and Education, Karolinska Institutet & Department of Obstetrics and Gynecology, Södersjukhuset, Stockholm, Sweden; 10 Department of Obstetrics and Gynecology, Centro Hospitalar Lisboa Central, Lisbon, Portugal; 11 Preventive Gynecology Unit, Division of Gynecology, European Institute of Oncology IRCCS, Milan, Italy; 12 Department of Perinatology and Oncological Gynecology, School of Health Sciences in Katowice, Medical University of Silesia, Katowice, Poland; 13 Department of Gynecological Oncology, National Cancer Institute of Milan, Milan, Italy; 14 Departments of Obstetrics and Gynecology, Clinica Universidad de Navarra, School of Medicine, Pamplona, Spain; 15 Department of Obstetrics and Gynecology, Biomedical and Clinical Sciences Institute L. Sacco, University of Milan, Milan, Italy; 16 Institute for Maternal and Child Health - IRCCS "Burlo Garofolo", Trieste, Italy; 17 Imaged Based Gynecology Service, Department of Obstetrics and Gynecology, University of South Florida Morsani College of Medicine, Tampa, Florida, United States; 18 Department of Obstetrics and Gynecology, University of Florence, Florence, Italy; 19 Department of Obstetrics and Gynecology, University of Cagliari, Policlinico Universitario Duilio Casula, Monserrato, Cagliari, Italy; 20 Department of Obstetrics and Gynecology, Whipps Cross Hospital, London, UK; 21 Department of Obstetrics and Gynecology, Ikazia Hospital, Rotterdam, The Netherlands; 22 Department of Oncology, Leuven Cancer Institute, Laboratory of Tumor Immunology and Immunotherapy, ImmunOvar Research Group, KU Leuven, Leuven, Belgium; 23 Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK; 24 Department of Public Health and Primary Care, KU Leuven, Belgium; 25 Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, Netherlands

Corresponding author:

Dirk Timmerman

KU Leuven, Department of Development and Regeneration

Herestraat 49 box 7003

3000 Leuven

Belgium

T 0032 16 344201

E [dirk.timmerman@uzleuven.be](mailto:dirk.timmerman@uzleuven.be)

## Abstract

**Background** - Traditionally ovarian tumours have been surgically removed because of the presumed risk of complications. Large prospective studies on long-term follow-up of adnexal masses are lacking. The aim is to estimate the cumulative incidence of cyst accidents (torsion, rupture) and malignancy during the first two years of follow-up of adnexal masses classified as benign using ultrasonography.

**Methods** – This is a 2-year interim analysis of a multicentre international prospective cohort study (IOTA5 study) involving consecutive patients with an adnexal mass selected for surgery or conservative management after ultrasound assessment. Follow-up of patients managed conservatively is ongoing. This interim analysis focuses on patients selected for conservative management of an adnexal mass judged to be benign on ultrasound on the basis of subjective assessment of ultrasound images. Patients were recruited consecutively between January 1<sup>st</sup> 2012 and March 1<sup>st</sup> 2015 in 36 centres. We analysed follow-up information until June 30<sup>th</sup> 2017. All patients had at least one adnexal mass and underwent a standardised transvaginal ultrasound examination. The primary endpoint is cumulative incidence of spontaneous resolution of the mass, and torsion, cyst rupture, borderline or invasive malignancy confirmed surgically in patients with a newly diagnosed adnexal mass.

**Findings** – The analysis comprises 3144 patients selected for conservative management of an adnexal mass judged to be benign on ultrasound. For 221 patients (7%) we have incomplete data, 336 (11%) patients were operated on before a planned follow-up scan was performed. Of 2587 patients with follow-up, 668 (26%) had a mass already being followed at the same centre before recruitment, and 1919 (74%) presented with a new mass (not already in follow-up in the centre before recruitment; median follow-up of the latter 27 months). The cumulative incidence of spontaneous resolution within 2 years of follow-up (n=1919) was 20.2% (95% CI, 18.4-22.1), that of invasive malignancy, borderline tumour, torsion and cyst rupture was 0.4% (95% CI, 0.1-0.6%), 0.3% (95% CI, <0.1-0.5%), 0.4% (95% CI, 0.1-0.7%), and 0.2% (95% CI, <0.1-0.4%), respectively.

**Interpretation** – Knowledge that the risk of malignancy and acute complications is low if adnexal masses with benign ultrasound morphology are managed conservatively is of great

value when counselling patients and supports conservative management of adnexal masses classified as benign using ultrasound.

Funding – Research Foundation Flanders, KU Leuven, Swedish Research Council.

## INTRODUCTION

The management of an adnexal mass is an important clinical problem. It is estimated that more than 200,000 women undergo exploratory surgery for a pelvic mass in the USA each year, and that 22,240 patients will be diagnosed with ovarian cancer in 2018.<sup>1,2</sup> Due to the widespread use of diagnostic imaging, including ultrasound, adnexal masses are often detected incidentally, and most of them will prove to be benign.<sup>3,4</sup> Traditionally most women with an adnexal mass undergo surgery. The probable reason for this liberal use of surgery is a concern that an adnexal mass may prove to be malignant or that it will undergo malignant transformation if left in situ. A further issue is the presumed risk of torsion or rupture of the mass. Women are likely to benefit from surgical removal of an adnexal mass if there are bothersome symptoms related to it, or from being referred to a gynaecologic oncologist for evaluation before surgery if there is a suspicion of malignancy.<sup>5</sup> However, surgical interventions for asymptomatic patients with benign adnexal masses are expensive and also associated with complications. The reported rate of severe surgical complications for incidentally detected benign adnexal masses varies from 3.5% to as high as 15%.<sup>4,6</sup> Conservative management might be an alternative for asymptomatic benign adnexal masses, but large studies describing long-term follow-up are lacking, and so the natural history of adnexal masses left in situ is largely unknown. This lack of knowledge makes the management of adnexal masses in asymptomatic women or women with minimal symptoms clinically challenging.

In contrast to Magnetic Resonance and Computed Tomography imaging, ultrasonography is cheap, harmless, accessible, requires no preparation of patients and there are no contraindications. Both subjective assessment of ultrasound images and the International Ovarian Tumour Analysis (IOTA) ultrasound algorithms are excellent methods to discriminate between benign and malignant adnexal masses.<sup>7-9</sup> This would suggest that ultrasound is the preferred method for following up patients with an adnexal mass judged not to require surgery. To date, however, it is unknown whether a benign appearance on ultrasound means it is safe to manage an adnexal mass expectantly.

The aim of this study is to estimate the risk of adverse events (including a diagnosis of malignancy, cyst rupture, or torsion) during ultrasound follow-up of adnexal masses with benign ultrasound morphology in patients with no or minimal symptoms.

## **METHODS**

### **Study design and participants**

This is a 2-year interim analysis of the IOTA5 study, an international multicentre prospective cohort study (for details see IOTA5 project plan in Supplementary material p19). IOTA5 includes consecutive patients with an adnexal mass selected for surgery or conservative management after ultrasound assessment. The patients were recruited from January 1<sup>st</sup>, 2012 to December 31<sup>st</sup>, 2016. The study will continue at least until five years of follow-up for each conservatively managed patient is achieved. The primary aim of the IOTA5 study is to estimate the risk of adverse events during ultrasound follow-up of adnexal masses with benign ultrasound morphology. We obtained approval from the ethics committee of the University Hospitals Leuven as the coordinating centre (B32220095331/S51375), and the local ethics committee of each contributing centre.

Due to lack of evidence in the literature, it was desirable to have an interim analysis while the study was ongoing, in order to estimate the incidence of complications during follow-up. Most false negative results should be detected within one year of follow-up. During the second year of follow-up malignant transformations could become more frequent. Hence, we here report outcomes during the first two years of ultrasound follow-up of patients selected for conservative management with an adnexal mass judged to be benign on ultrasound. For this interim analysis we include patients recruited between January 1<sup>st</sup>, 2012 and March 1<sup>st</sup>, 2015 and follow-up data until June 30<sup>th</sup>, 2017. Thirty-six centres in 14 countries recruited patients to the study. The contributing centres were either oncology referral centres (tertiary centres with a specific gynaecologic oncology unit) or other types of centre. Patients were eligible if they were at least 18 years old at recruitment, and presented with at least one adnexal mass (ovarian, para-ovarian or tubal) on ultrasound examination. Pending informed consent, local clinicians examined the patient following a standardised research protocol. Exclusion criteria were lesions presumed to be physiological if <3 cm in largest diameter, denial or withdrawal of informed consent. Pregnancy was not an exclusion criterion. Patients could be recruited into the study even if they had an adnexal mass that was already being followed up in the recruitment centre. If so, the time in follow-up before inclusion was registered.

Because no accurate estimates of study outcomes could be found in the literature we stated in the IOTA5 project plan that we aimed to collect at least 3000 patients with an adnexal mass and at least 1000 patients with an adnexal mass managed conservatively.

## **Procedures**

The ultrasound examiners recruiting patients collected clinical information and performed a transvaginal ultrasound examination following the standardised research protocol. They used grey scale and colour or power Doppler ultrasound to characterize the morphology and vascularisation of the adnexal mass and described the ultrasound results using IOTA terminology.<sup>10</sup> There were no requirements about level of experience of the ultrasound examiners, but all investigators had passed the IOTA certification test<sup>11</sup> and were required to submit five representative ultrasound images for approval of image quality before recruiting patients. The ultrasound examiner classified each mass using subjective assessment of the ultrasound images as benign, borderline or malignant and specified the degree of certainty with which the diagnosis was made (certainly - probably - uncertain). The presumed histology was also registered. The ultrasound diagnoses were based on knowledge of the typical ultrasound appearance of benign, borderline and malignant lesions and that of different types of specific adnexal pathology.<sup>12</sup> When the examiner detected multiple masses, the dominant mass was defined as the mass with the most complex ultrasound morphology. If multiple masses had similar morphology, the largest mass or the one best accessible with ultrasound was denoted dominant. The dominant mass was used for outcome assessment. The ultrasound examiner suggested surgery or conservative management on the basis of the ultrasound diagnosis (benign or malignant, borderline tumours considered malignant) and the patient's symptoms. Conservative management included ultrasound and clinical follow-up at intervals of three, six and then every 12 months. At follow-up visits clinical information including symptoms was collected and a transvaginal ultrasound examination following the research protocol was performed. In this analysis we include masses that were judged to be probably or certainly benign on the basis of subjective evaluation of the ultrasound images and that were selected for conservative management by the ultrasound examiner. Ultimately, the treating clinician decided upon management.

We collected the data through a secure electronic platform developed for the study (IOTA5 Study Screen; astraia Software, Munich, Germany). Patients automatically received a unique

identifier upon enrolment. We encrypted all data communication to ensure data security. A team of biostatisticians and expert ultrasound examiners performed data cleaning. Data cleaning included sending queries to participating centres to retrieve missing information. At the local centres a standardised questionnaire (Supplementary material p12) was used to accrue missing information by telephone contact to patients and managing clinicians.

## **Outcomes**

Follow-up continued until one of three study outcomes was observed: spontaneous resolution (the examiner could no longer visualize the mass in the absence of any surgical intervention), surgical removal of the mass, or death due to any cause. The indication for surgery was based on local practice. We classified the reason for surgery into three groups: 1) suspicion of malignancy, 2) pain, and 3) patient request, fertility concerns, opportunistic or prophylactic removal (Supplementary material p2). We classified the findings at surgery into six groups: 1) invasive malignancy, 2) borderline tumour, 3) torsion, 4) cyst rupture, 5) minor mass complications (inflammation/infection or adhesions), or 6) no mass complications (Supplementary material p2). Histological examination was performed at the local centre. We did not include central pathology review, because we previously observed little differences in reported outcomes between local and central pathology reports.<sup>13</sup> We classified malignant tumours according to the criteria recommended by the International Federation of Gynaecology and Obstetrics.<sup>14</sup>

The main study endpoints were cumulative incidence of spontaneous resolution of the mass, surgical confirmation of torsion or cyst rupture and histological confirmation of invasive malignancy or a borderline tumour within two years of study entry in patients with a new mass (not already in follow-up in the centre before recruitment).

## **Statistical analysis**

We calculated the follow-up time from the recruitment visit until the study outcome. In the absence of a study outcome, we calculated follow-up time until the last visit, and included these patients as censored observations in the analysis. We estimated median follow-up with the reverse Kaplan-Meier method.<sup>15</sup> We analysed follow-up data using cumulative incidence



curves in the context of competing risks survival analysis.<sup>16</sup> Cumulative incidence curves for a specific outcome classified other outcomes as competing events. We summarized cumulative incidence curves by reporting the estimated cumulative incidence with 95% confidence intervals at 12 months and 24 months of follow-up. Some patients underwent surgery before they had undergone a follow-up scan, even though the ultrasound examiner had suggested conservative management. We did not include these patients in the survival analysis, but we describe the reason for surgery and the histological outcome for them separately. For other patients, we did not have any information after the initial visit. These patients provide no information and were not included in the survival analysis. We present descriptive statistics separately for patients without any information (i.e. patients lost to follow-up before any follow-up scan was performed) and for patients with information after recruitment (i.e. patients with follow-up scans or operated on before a follow-up scan was performed) to check for differences in background information between these groups.

The main analysis is the survival analysis performed only on patients with a new mass (a mass that was not already in follow-up in the centre before recruitment). This provides the most correct estimates of cumulative incidences by avoiding survival bias (masses already in follow-up before recruitment are a selected group with probably a higher proportion of benign and stable tumours). To provide transparent reporting of all data in our study, we also show the results of survival analysis performed on all patients.

Finally, we performed a subgroup analysis for the variable menopausal status at recruitment, where we report cumulative incidences at 12 and 24 months of follow-up. If menopausal status was uncertain (for example because of hysterectomy), we classified patients aged 50 years or older as postmenopausal.

The statistical analysis was performed with R version 3.4.4.

### **Role of the funding source**

The funders had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## RESULTS

In total, 8519 patients were recruited into IOTA5 between January 1<sup>st</sup>, 2012 and March 1<sup>st</sup>, 2015 (Figure 1). We excluded 25 patients following withdrawal of consent. The ultrasound examiner suggested conservative management for 4567 patients, of which 4447 (97%) were judged to have a mass that was probably or certainly benign (Supplementary material p3-4). The ultrasound examiner suggested conservative management for 3602 (49%) of the patients with a new mass, of which 3494 (97%) were judged to have a mass that was probably or certainly benign. We excluded 17 centres because they recruited too few patients or provided follow-up data of insufficient quality (Supplementary material p3-4). Of the 3144 patients in the remaining 19 centres (Table 1), 734 (23%) patients had a mass that was already being followed in the recruitment centre before inclusion and 2410 (77%) had a new mass (Table 2).

Median age of the 3144 patients was 48 years (interquartile range 37-63), 1429 patients (45%) were postmenopausal, 1912 (61%) had a dominant mass that was a unilocular cyst (one cyst locule, no solid components) and 444 (14%) had a dominant mass containing solid components (Table 2).<sup>10</sup> For 221/3144 (7%) patients, we have no follow-up information after the recruitment visit (Table 1), of which 177 had a new mass (see Supplementary material p5 for descriptive statistics). Even though conservative management was suggested, 336/3144 (11%) patients were operated on before any follow-up visit, of which 314 had a newly diagnosed mass (Table 2). Of these 314, 13 (4%) were operated on because of suspicion of malignancy by the managing clinician and 113 (36%) because of pain (Table 3). Median time between recruitment scan and surgery in the 314 patients was 2 months (range 0-47, interquartile range 1-4). Stage III primary ovarian cancer was found in one (<1%) patient, stage I borderline tumours in two (1%), torsion in seven (2%), and cyst rupture in six (2%) patients (Table 3).

For the 1919 patients with a new mass that actually received follow-up, median follow-up was 27 months (interquartile range, 14-38). A histogram showing the follow-up time at all patient visits can be found in Supplementary material p10. For patients with a new mass (n = 1919), the 2-year cumulative incidence for spontaneous resolution was 20.2% (95% CI, 18.4-22.1), 16.1% (95% CI, 14.3-17.7) for any surgical intervention (Table 4, Figure 2) and 2.0% (95% CI, 1.3-2.6) for surgical intervention because of suspected malignancy (Table 4, Supplementary material p11). The 2-year cumulative incidences of finding invasive

malignancy, a borderline tumour, torsion, or cyst rupture at surgery were 0.4% (95% CI, 0.1-0.6), 0.3% (95% CI, <0.1-0.5), 0.4% (95% CI, 0.1-0.7), and 0.2% (95% CI, <0.1-0.4), respectively (Table 4, Figure 3). Among these 1919 patients, we observed the following complications within 24 months of follow-up: seven invasive malignancies (three stage I, two stage III, two secondary metastatic tumours), five borderline tumours, seven torsions, and four cyst ruptures. Six of the malignancies were diagnosed with surgery within three months after inclusion, three after four to six months, two after 11 months, and one after 20 months (Supplementary material p6-7).

The subgroup analysis for pre- and postmenopausal patients who presented with a new mass is shown in Supplementary material p8. The absolute number of patients undergoing surgery during the first two years of follow-up was 192 and 96 for pre- and post-menopausal patients, respectively.

In Supplementary material p9, we report the cumulative incidences of study outcomes at 12 and 24 months for patients of all centres, including the 17 centres excluded because they recruited too few patients or provided follow-up data of insufficient quality.

## DISCUSSION

Among patients selected for conservative management of an adnexal mass with benign ultrasound morphology, the two-year cumulative incidence was 20.2% for spontaneous resolution and 16.1% for surgical intervention. The overall two-year cumulative incidence of complications was low: 0.4% for invasive malignancy, 0.3% for borderline tumours, 0.4% for torsion, and 0.2% for cyst rupture.

To the best of our knowledge, this is the largest prospective study describing the outcome of consecutively recruited conservatively managed adnexal masses. In contrast to most other prospective cohort studies<sup>17-24</sup>, we report results for all patients, including those operated on before a follow-up visit despite them having been selected for conservative management. A large number of ultrasound centres and operators from different countries and with different levels of experience participated, which increases the likelihood of our results being generalisable. We applied thorough data cleaning to achieve reliable data, and we present our results as cumulative incidences based on survival analysis.

Unfortunately, a proportion of the patients selected for expectant management was excluded or censored in the survival analysis because of loss to follow-up. However, loss to follow-up reflects clinical reality. For example, some of the patients referred to a study site for a second opinion that were selected for follow-up later opted for management at their primary centre because of travel distances or other logistical problems, whilst others moved to another city or another country. We made great efforts to minimize loss to follow-up (several rounds of queries to study sites and managing clinicians, structured telephone interviews with patients) and we included only centres with sufficient quantity and quality of follow-up data in our primary analysis. We do not believe that loss to follow-up has resulted in major bias, because there were no important differences in patient or tumour characteristics between patients with and without follow-up information (Supplementary material p5).

The low risk of complications we have observed shows that conservative management with clinical and ultrasound follow-up of adnexal masses with a benign ultrasound appearance is a safe management option. In contrast to most previously published studies on follow-up of

adnexal masses<sup>17-32</sup>, our study is prospective, large, multicentre, had very broad inclusion criteria and to the best of our knowledge it is the only study that uses survival analysis to estimate the risk of complications. It provides the most solid evidence to date of the natural history of adnexal masses left in situ.

Our results are not directly comparable to those in the literature due to differences in inclusion criteria, follow-up time and study outcomes. However, in agreement with our results, torsion of an adnexal lesion during follow-up is rare in published studies.<sup>17,18,22,25,28,29</sup> To the best of our knowledge, no published study has reported on cyst rupture. The results of our subgroup analysis in premenopausal patients are similar to those in the largest (166 patients) single-centre study in a comparable population.<sup>18</sup> After at least 1 year of follow-up in 134 postmenopausal patients, Valentin and Akrawi reported a higher rate of spontaneous resolution (29.1%) and a lower rate of surgery (9.0%) than in our study.<sup>19</sup> The discrepancy might be explained at least partly by differences in size and ultrasound morphology of the lesions between the two studies. The difference in the rate of surgery between pre- and postmenopausal patients observed in our study may be explained by differences in indications for surgery. Premenopausal patients more often undergo surgery because of pain. They often have endometriomas causing pain, while endometriomas are rarely symptomatic in postmenopausal patients. The most common indication for surgery during follow-up was 'patient request, fertility concerns, opportunistic or prophylactic removal'. Because operative risks are generally higher in old than young women, postmenopausal women are less prone to request surgery than premenopausal women and doctors are more reluctant to perform surgery on old than young women.

The clinical challenge is to balance any possible benefit of removing presumably benign adnexal masses in women with no or minimal symptoms against the risks of surgery. The presumed benefit of removing adnexal masses with benign ultrasound morphology is prevention of a benign lesion becoming malignant and avoiding leaving a malignant lesion in situ because of misdiagnosis. However, in an observational study, in which virtually all benign adnexal lesions detected at screening for ovarian cancer were surgically removed, ovarian cancer mortality was not lower than expected in the screened population after on average 15 years of follow-up.<sup>33</sup> Randomised trials on ovarian cancer screening, in which substantial numbers of benign lesions were surgically removed, have also not shown a reduction of ovarian cancer mortality.<sup>4,6</sup> The explanation is probably that ovarian borderline tumours and cancers that develop from benign lesions are Type I tumours (low-grade serous,

low-grade endometrioid, clear cell, and mucinous). These develop slowly, have a good prognosis and account for only a small proportion of ovarian cancer mortality. Type II tumours (high-grade serous and undifferentiated carcinomas, and malignant mixed mesodermal tumours) may arise from fallopian tube precursors, have aggressive behaviour and a less favourable prognosis.<sup>34</sup> Out of 1919 patients with a new adnexal mass managed conservatively in our study, five were diagnosed with ovarian cancer, five with an ovarian borderline tumour, and two with metastases in the ovaries from another primary tumour. All but one of the malignancies (a borderline tumour) were surgically removed within one year of follow-up, and nine of them within the first six months (Supplementary material p6-7). Four of the ovarian cancers were type I (three stage I and one stage III), and one was a type II ovarian cancer (stage III) (Supplementary material p6-7). The short time interval between recruitment of these patients and diagnosis of malignancy at surgery suggests that these cases might represent initial misdiagnosis. Moreover, retrospective review of the ultrasound images of the malignant lesions showed that many of them manifested ultrasound signs suspicious for malignancy at inclusion and so were misdiagnosed as benign. We find it unlikely that the prognosis of the borderline tumours and stage I tumours was made worse by the delay of diagnosis. It is difficult to know if and to what extent the prognosis of the two stage III ovarian cancers and the two secondary cancers was affected. Longer follow-up than in this analysis is needed to estimate the incidence of a change from benign to malignant ultrasound morphology in an adnexal mass. The disadvantage of performing surgery on all adnexal masses is the risk of short term and long term surgical complications. The reported rates of severe surgical complications (e.g. injury to hollow viscus, deep vein thrombosis, pulmonary embolism, wound breakdown, bowel obstruction, myocardial infarction) associated with removal of benign adnexal masses detected at screening for ovarian cancer in women 50 to 74 years old are 15.1% (163/1080) and 3.5% (57/1634).<sup>4,6</sup> For our own study population, we do not have complete information on intra-operative and post-operative surgical complications. If the published complication rates apply to our postmenopausal population, and if we had operated on all 823 postmenopausal women with a new adnexal mass in our study, then 29 to 123 of them would have suffered severe surgical complications. Instead, only 96 of them (12%) underwent surgery, which means that severe complications were probably avoided in between 26 and 109 postmenopausal women. The complication rate associated with adnexal surgery in premenopausal women is not well known but is probably lower than in postmenopausal women. In addition to intra-operative and postoperative complications there

are long term complications, e.g. adhesion formation that may cause bowel obstruction, chronic pelvic pain, or fertility problems.

The international multicentre nature of the study and the consecutive recruitment of a large number of patients by investigators with different levels of experience make our results highly likely to be generalisable. As many as 49.1% of the patients with a newly diagnosed adnexal mass were deemed suitable for conservative management at the first visit. However, the proportion of patients judged to be suitable for follow-up differed between the centres in our study, probably due to differences in patient characteristics and level of experience of ultrasound examiners. Not only the ultrasound morphology of an adnexal mass dictates management. There may be clinical reasons to opt for conservative management, such as comorbidity making the patient unfit for surgery, or previous adnexal surgery resulting in reduced ovarian reserve in a premenopausal patient. Based on the results of this interim analysis with two years of follow-up, adnexal masses presumed to be benign on ultrasound seem suitable for ultrasound and clinical follow-up at intervals of three, six and then 12 months. Before management recommendations can be made for longer follow-up than two years we need to await results on extended follow-up of our conservatively managed patients. Future research should also investigate whether the application of objective criteria or prediction models could improve safe selection of patients for follow-up.

## **CONCLUSION**

Knowledge that the risk of malignancy and acute complications is low if adnexal masses with benign ultrasound morphology are managed conservatively is of great value when counselling patients and supports conservative management of adnexal masses classified as benign using ultrasound. This information may lead to a substantial reduction in the number of women who undergo surgery for benign adnexal pathology.



## **CONTRIBUTORS**

DT, LV, AT, TB and BVC conceived and designed the study. DT, LV, AT, TB, WF, CL, PS, CVH, ED, RF, EE, MJDSB, DF, MJK, VC, JLA, FPL, FB, LH, MEC, SG, ND, LJ, JK and AC enrolled patients and acquired data. DT, BVC, WF, CL and BDC were involved in data cleaning. DT, LV, TB, BVC, BDC and WF wrote the Statistical Analysis Plan. BVC and BDC analysed the data, with support from LW and JYV. DT, LV, AT, TB, BVC, WF, CL, BDC, LW and JYV were involved in data interpretation. DT, LV, AT, TB, BVC, WF, CL, BDC, LW and JYV wrote the first draft of the manuscript, which was then critically reviewed and revised by the other co-authors. All authors approved the final version of the manuscript for submission. DT and BVC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## **DECLARATION OF INTERESTS**

The authors have no conflicts of interest to declare in relation to this study. Tom Bourne reports grants, personal fees and other from Samsung Medison, other from Roche Diagnostics, personal fees from GE Healthcare, outside the submitted work.

## **ACKNOWLEDGMENTS**

We thank all medical specialists, data and case managers, secretaries, and all other people who collected all data necessary for completing the database. In particular, we want to thank Artur Czekierdowski, Daniela Fischerova, Mona Aboulghar, Ulrike Metzger, Anna Knafel, Chiara Lanzani, Fatima Alves, Thierry Van den Bosch, Samir Helmy, Alberto Rossi, and Maria Angela Pascual.

The IOTA5 study is supported by the Research Foundation–Flanders (FWO) projects G049312N/G0B4716N/12F3114N, and Internal Funds KU Leuven (project C24/15/037). Dirk Timmerman is a senior clinical investigator of FWO. Tom Bourne is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed are those of the authors and not necessarily those of the NHS, NIHR or Department of Health. Lil Valentin is supported by the Swedish Research Council (grant K2014-99X-22475-01-3, Dnr 2013-02282), funds administered by Malmö University Hospital and Skåne University Hospital, Allmänna Sjukhusets i Malmö Stiftelse för bekämpande av cancer (the Malmö

General Hospital Foundation for fighting against cancer), and two Swedish governmental grants (Avtal om läkarutbildning och forskning (ALF)-medel and Landstingsfinansierad Regional Forskning). The sponsors had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the work for publication. The researchers performed this work independently of the funding sources.

## References

1. Curtin JP. Management of the Adnexal Mass. *Gynecologic Oncology* 1994;**55**:S42-S6.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;**68**:7-30.
3. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 2009;**10**:327-40.
4. Buys SS, Partridge E, Black A, et al. Effect of Screening on Ovarian Cancer Mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA* 2011;**305**:2295.
5. Woo YL, Kyrgiou M, Bryant A, Everett T, Dickinson HO. Centralisation of services for gynaecological cancers - a Cochrane systematic review. *Gynecol Oncol* 2012;**126**:286-90.
6. Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *The Lancet* 2016;**387**:945-56.
7. Meys EM, Kaijser J, Kruitwagen RF, et al. Subjective assessment versus ultrasound models to diagnose ovarian cancer: A systematic review and meta-analysis. *Eur J Cancer* 2016;**58**:17-29.
8. Van Calster B, Van Hoorde K, Valentin L, et al. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. *BMJ* 2014;**349**:g5920.
9. Timmerman D, Van Calster B, Testa A, et al. Predicting the risk of malignancy in adnexal masses based on the Simple Rules from the International Ovarian Tumor Analysis group. *Am J Obstet Gynecol* 2016;**214**:424-37.
10. Timmerman D, Valentin L, Bourne T, Collins WP, Verrelst H, Vergote I. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) group. *Ultrasound Obstet Gynecol* 2000;**16**:500-5.
11. <http://www.iotagroup.org/index.php/certified-members> access date September 25th 2018.
12. Valentin L. Use of morphology to characterize and manage common adnexal masses. *Best Pract Res Clin Obstet Gynaecol* 2004;**18**:71-89.
13. Timmerman D, Testa AC, Bourne T, et al. Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International Ovarian Tumor Analysis Group. *J Clin Oncol* 2005;**23**:8794-801.
14. Heintz APM, Odicino F, Maisonneuve P, et al. Carcinoma of the Ovary. *International Journal of Gynecology & Obstetrics* 2006;**95**:S161-S92.
15. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Controlled Clinical Trials* 1996;**17**:343-6.
16. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res* 2007;**13**:559-65.
17. Alcazar JL, Castillo G, Jurado M, Garcia GL. Is expectant management of sonographically benign adnexal cysts an option in selected asymptomatic premenopausal women? *Hum Reprod* 2005;**20**:3231-4.
18. Alcazar JL, Olartecoechea B, Guerriero S, Jurado M. Expectant management of adnexal masses in selected premenopausal women: a prospective observational study. *Ultrasound Obstet Gynecol* 2013;**41**:582-8.

19. Valentin L, Akrawi D. The natural history of adnexal cysts incidentally detected at transvaginal ultrasound examination in postmenopausal women. *Ultrasound Obstet Gynecol* 2002;**20**:174-80.
20. Castillo G, Alcazar JL, Jurado M. Natural history of sonographically detected simple unilocular adnexal cysts in asymptomatic postmenopausal women. *Gynecol Oncol* 2004;**92**:965-9.
21. Aubert JM, Rombaut C, Argacha P, Romero F, Leira J, Gomez-Bolea F. Simple adnexal cysts in postmenopausal women: conservative management. *Maturitas* 1998;**30**:51-4.
22. Caspi B, Appelman Z, Rabinerson D, Zalel Y, Tulandi T, Shoham Z. The growth pattern of ovarian dermoid cysts: a prospective study in premenopausal and postmenopausal women. *Fertil Steril* 1997;**68**:501-5.
23. Auslender R, Atlas I, Lissak A, Bornstein J, Atad J, Abramovici H. Follow-up of small, postmenopausal ovarian cysts using vaginal ultrasound and CA-125 antigen. *J Clin Ultrasound* 1996;**24**:175-8.
24. Levine D, Gosink BB, Wolf SI, Feldesman MR, Pretorius DH. Simple adnexal cysts: the natural history in postmenopausal women. *Radiology* 1992;**184**:653-9.
25. Hoo WL, Yazbek J, Holland T, Mavrelou D, Tong EN, Jurkovic D. Expectant management of ultrasonically diagnosed ovarian dermoid cysts: is it possible to predict outcome? *Ultrasound Obstet Gynecol* 2010;**36**:235-40.
26. Suh-Burgmann E, Hung YY, Kinney W. Outcomes from ultrasound follow-up of small complex adnexal masses in women over 50. *Am J Obstet Gynecol* 2014;**211**:623 e1-7.
27. Goldstein S, Subramanyam B, Snyder JR, Beller U, Raghavendra BN, Beckman EM. The postmenopausal cystic adnexal mass: the potential role of ultrasound in conservative management. *Obstet Gynecol* 1989;**73**:8-10.
28. Alcazar JL, Pascual MA, Marquez R, et al. Malignancy risk of sonographically benign appearing purely solid adnexal masses in asymptomatic postmenopausal women. *Menopause* 2017;**24**:613-6.
29. Pascual MA, Graupera B, Pedrero C, et al. Long-term Results for Expectant Management of Ultrasonographically Diagnosed Benign Ovarian Teratomas. *Obstet Gynecol* 2017;**130**:1244-50.
30. Sarkar M, Wolf MG. Simple ovarian cysts in postmenopausal women: scope of conservative management. *Eur J Obstet Gynecol Reprod Biol* 2012;**162**:75-8.
31. Nardo LG, Kroon ND, Reginald PW. Persistent unilocular ovarian cysts in a general population of postmenopausal women: is there a place for expectant management? *Obstet Gynecol* 2003;**102**:589-93.
32. Kroon E, Andolf E. Diagnosis and follow-up of simple ovarian cysts detected by ultrasound in postmenopausal women. *Obstet Gynecol* 1995;**85**:211-4.
33. Crayford TJB, Campbell S, Bourne TH, Rawson HJ, Collins WP. Benign ovarian cysts and ovarian cancer: a cohort study with implications for screening. *The Lancet* 2000;**355**:1060-3.
34. Kurman RJ, Shih Ie M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol* 2010;**34**:433-43.

**Table 1. Patients with a mass judged to be benign and selected for conservative management included in the study.**

Centre	N	Without follow-up information n (%)	Operated before any follow-up n (%)
Malmo, Sweden	674	16 (2%)	67 (10%)
Leuven, Belgium	377	12 (3%)	14 (4%)
Rome, Italy	316	40 (13%)	44 (14%)
Genk, Belgium	245	24 (10%)	43 (18%)
Athens, Greece	211	24 (11%)	97 (46%)
Monza, Italy	209	32 (15%)	10 (5%)
Stockholm, Sweden	166	4 (2%)	16 (10%)
Lisbon, Portugal	140	0	8 (6%)
Milan, Italy	125	9 (7%)	0
Katowice, Poland	98	10 (10%)	8 (8%)
Pamplona, Spain	95	19 (20%)	10 (10%)
London, UK	83	2 (2%)	2 (2%)
Milan 2, Italy	82	2 (2%)	3 (4%)
Milan 3, Italy	82	7 (8%)	1 (1%)
Florence, Italy	62	7 (11%)	4 (6%)
Trieste, Italy	59	0	4 (7%)
Tampa, USA	58	6 (10%)	0
Cagliari, Italy	42	4 (9%)	2 (5%)
Nottingham, UK	20	3 (15%)	3 (15%)
Total	3144	221 (7%)	336 (11%)

**Table 2. Descriptive statistics.**

Variable	All patients (n=3144)	New masses (n=2410) <sup>c</sup>	New masses with actual follow-up (n=1919)	Masses already in follow-up (n=734) <sup>c</sup>
Patient age at recruitment (years)	48 (37-63), 18-98	47 (35-61), 18-98	48 (36-62), 18-98	55 (42-67), 18-93
Postmenopausal	1429 (45%)	1001 (41%)	823 (43%)	428 (58%)
Gynaecological symptoms during the year preceding inclusion	1760 (56%)	1358 (56%)	1069 (56%)	402 (55%)
Time in follow-up at recruitment (months)				18 (6-36), 0-25-266
Tumour type using IOTA terminology <sup>10</sup>				
Unilocular	1912 (61%)	1474 (61%)	1149 (60%)	438 (60%)
Unilocular-solid	138 (4%)	97 (4%)	79 (4%)	41 (6%)
Multilocular	788 (25%)	601 (25%)	505 (26%)	187 (25%)
Multilocular-solid	122 (4%)	96 (4%)	80 (4%)	26 (3%)
Solid	184 (6%)	142 (6%)	106 (5%)	42 (6%)
Presence of solid components	444 (14%)	335 (14%)	265 (14%)	109 (15%)
Maximum diameter of lesion (mm)	41 (30-55), 5-456	42 (30-56), 7-456	41 (30-54), 7-216	40 (29-53), 5-157
Bilateral masses	359 (11%)	269 (11%)	212 (11%)	90 (12%)
Ultrasound examiner's subjective impression				
Certainly benign	2282 (73%)	1716 (71%)	1336 (70%)	566 (77%)
Probably benign	862 (27%)	694 (29%)	583 (30%)	168 (23%)
Ultrasound examiner's presumed diagnosis				
Simple/para-ovarian/salpingeal cyst	762 (24%)	583 (24%)	480 (25%)	179 (24%)
Serous cystadeno(fibr)oma	744 (24%)	511 (21%)	428 (22%)	233 (32%)
Endometrioma	591 (19%)	458 (19%)	331 (17%)	133 (18%)
Teratoma	347 (11%)	268 (11%)	195 (10%)	79 (11%)
Functional cyst	182 (6%)	177 (7%)	158 (8%)	5 (1%)
Fibro(theco)ma	158 (5%)	116 (5%)	92 (5%)	42 (6%)
Hydrosalpinx	128 (4%)	104 (4%)	85 (4%)	24 (3%)
Mucinous cystadeno(fibr)oma	105 (3%)	84 (3%)	67 (3%)	21 (3%)
Abscess / salpingitis / PID	37 (1%)	34 (1%)	21 (1%)	3 (<1%)
Inclusion/peritoneal cyst	36 (1%)	26 (1%)	20 (1%)	10 (1%)
Rare benign tumour	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
Not possible	51 (2%)	47 (2%)	41 (2%)	4 (<1%)
Operated on before any follow-up scan	336 (11%)	314 (13%)	0	22 (3%)
Outcome events observed within 24 months after inclusion <sup>a</sup>				
Spontaneous resolution	406	374	374	32
Surgery performed	685	598	288	87
Invasive malignancy	11	8	7	3
Borderline tumour	9	7	5	2
Torsion	16	14	7	2
Cyst rupture	12	10	4	2
Minor mass complications <sup>b</sup>	113	97	47	16
No mass complications	524	462	218	62
Death any cause	27	20	20	7

Results are shown as median (interquartile range), min-max for continuous variables, and as n (%) for categorical variables.

<sup>a</sup> We do not provide percentages here, because these do not take follow-up time into account.

<sup>b</sup> Includes inflammation/infection or adhesions

<sup>c</sup> Includes patients without follow-up after inclusion in the study

**Table 3. Reason for surgery and histology/surgical findings in patients presenting with a new adnexal mass judged to be benign on the basis of ultrasound findings and selected for conservative management but operated on before a follow-up visit (n=314).**

Surgery findings	N	Reason for surgery			Months between recruitment scan and surgery <sup>b</sup>
		Suspicion of malignancy	Pain	Other <sup>a</sup>	
Major mass complications					
Primary invasive stage III	1	0	0	1	2
Borderline stage I	2	0	0	2	2 and 3
Benign histology with torsion	7	0	6	1	1 (0-3)
Benign histology with rupture	6	0	2	4	2.5 (0-7)
No major mass complications					
Endometrioma	75	2	48	25	2 (1-4)
Simple/parasalpingeal cyst	67	1	19	47	1 (0-3)
Serous cystadenoma	48	4	9	35	2 (1-3)
Teratoma	46	1	9	36	2.5 (1-5)
Mucinous cystadenoma	16	2	6	8	2 (1.75-3.5)
Hydrosalpinx / salpingitis	14	0	9	5	1 (0-2)
Physiological cyst	13	1	0	12	1 (0-2)
Fibroma	12	1	2	9	1 (1-2)
Abscess	3	0	2	1	0, 3 and 14
Peritoneal pseudocyst	2	0	1	1	0 and 5
Rare benign / no specific histology	2	1	0	1	0 and 6
All	314	13	113	188	2 (range 0-47)

<sup>a</sup> Includes patient request/fertility concerns/opportunistic/prophylactic

<sup>b</sup> For three or fewer cases the individual numbers are shown, for four or more cases median and range are shown

**Table 4. Outcome presented as cumulative incidences at 12 and 24 months**

Finding	All masses (n = 2587)		New masses (n = 1919)	
	12 months	24 months	12 months	24 months
Cumulative incidence by study outcome				
Spontaneous resolution of cyst	13.2 (11.8-14.5)	16.3 (14.8-17.7)	16.5 (14.8-18.2)	20.2 (18.4-22.1)
Surgery performed	9.0 (7.9-10.2)	14.6 (13.2-16.0)	10.3 (8.9-11.7)	16.1 (14.3-17.7)
Death of any cause	0.5 (0.2-0.7)	1.1 (0.7-1.6)	0.5 (0.2-0.8)	1.2 (0.6-1.7)
Cumulative incidence of surgery by indication				
Suspicion of malignancy	1.4 (0.9-1.8)	2.1 (1.6-2.7)	1.4 (0.9-2.0)	2.0 (1.3-2.6)
Pain	2.6 (1.9-3.2)	4.2 (3.4-5.0)	2.6 (1.9-3.4)	4.5 (3.5-5.5)
Patient request/fertility concerns/opportunistic or prophylactic removal	5.1 (4.2-6.0)	8.2 (7.1-9.3)	6.2 (5.1-7.3)	9.5 (8.2-10.9)
Cumulative incidence of surgery by outcome				
Invasive malignancy	0.3 (0.1-0.5)	0.4 (0.2-0.7)	0.4 (0.1-0.6)	0.4 (0.1-0.6)
Borderline tumour	0.2 (<0.1-0.4)	0.3 (0.1-0.5)	0.2 (<0.1-0.4)	0.3 (<0.1-0.5)
Torsion	0.2 (<0.1-0.4)	0.3 (0.1-0.6)	0.3 (<0.1-0.5)	0.4 (0.1-0.7)
Cyst rupture	0.2 (<0.1-0.4)	0.2 (<0.1-0.4)	0.2 (<0.1-0.3)	0.2 (<0.1-0.4)
Minor mass complications <sup>a</sup>	1.2 (0.8-1.6)	2.5 (1.8-3.1)	1.2 (0.7-1.8)	2.7 (2.0-3.5)
No mass complications	6.9 (5.9-7.9)	10.8 (9.6-12.1)	8.0 (6.8-9.2)	12.1 (10.5-13.6)
Probability of being in follow-up <sup>b</sup>	77.3 (75.6-78.9)	68.0 (66.1-69.8)	72.7 (70.6-74.6)	62.5 (60.2-64.7)

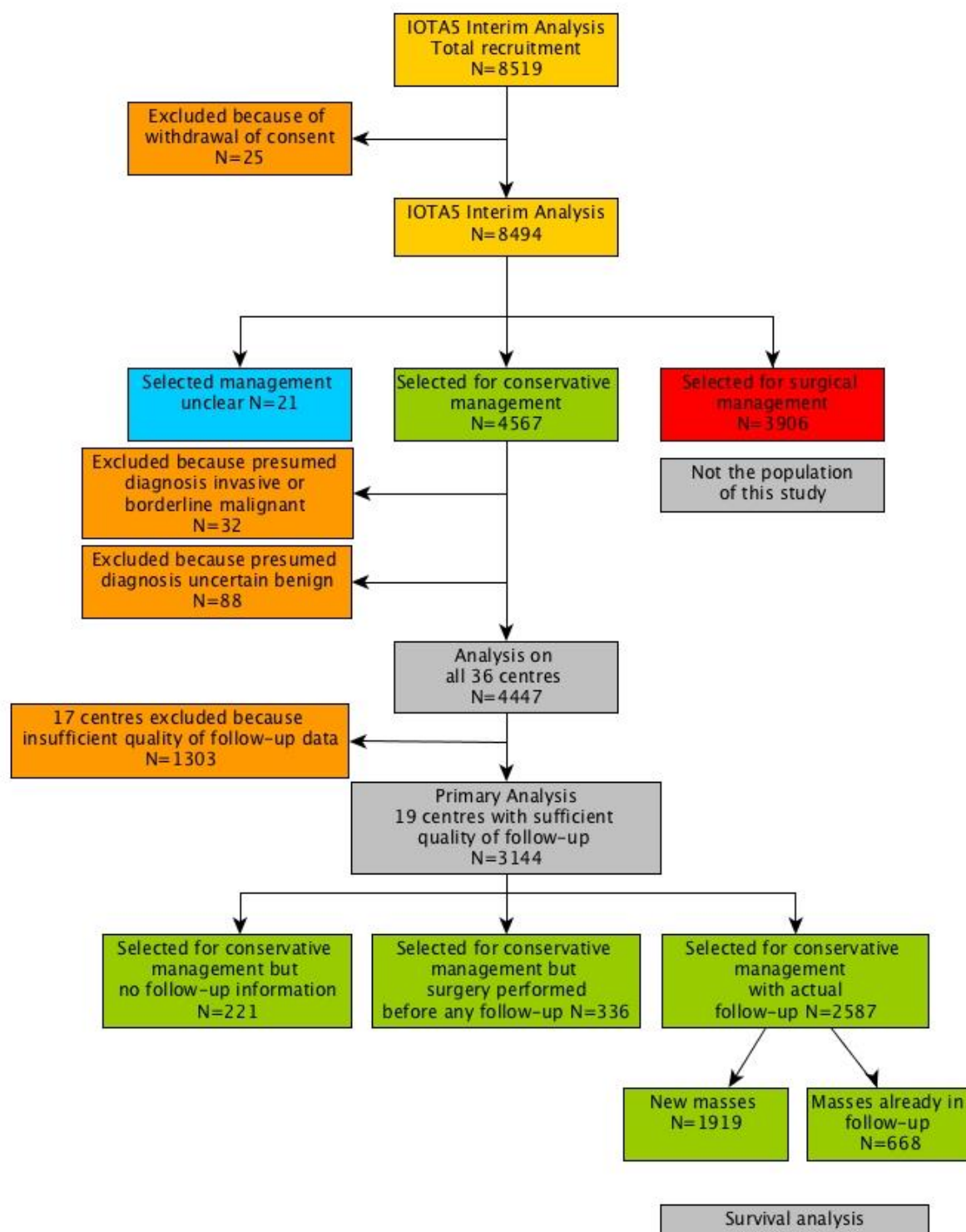
Cumulative incidence is shown as percent (95% confidence interval in brackets)

<sup>a</sup> Includes inflammation/infection or adhesions

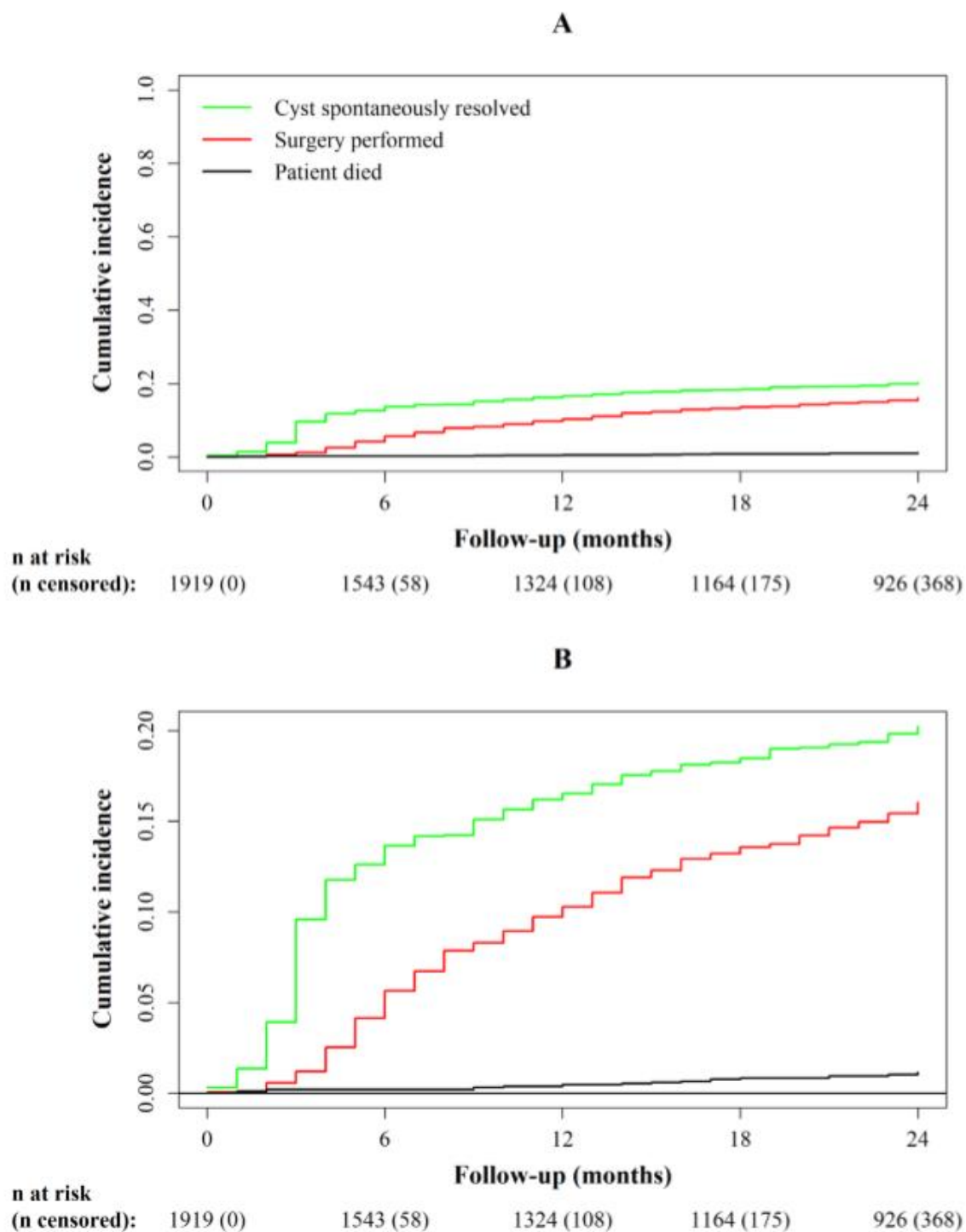
<sup>b</sup> The probability of being in follow-up at 12 months or 24 months is the estimated probability of not having a study outcome (spontaneous resolution, surgery, or death of any cause) after 12 or 24 months of conservative management. Therefore, it equals 100 minus the sum of the cumulative incidences of each study outcome.



**Figure 1. Flow chart.**



**Figure 2. Cumulative incidence curves of study outcome. This figure is based on patients who presented with a new mass and who actually received follow-up (n=1919). Panel A shows the full y-axis (from 0 to 1), panel B is a close up of the curves in panel A.**



**Figure 3. Cumulative incidence of surgery during follow-up, stratified by surgical outcome. This figure is based on patients who presented with a new mass and who actually received follow-up (n=1919). Panel A shows the full y-axis (from 0 to 1), panel B is a close up of the curves in panel A.**

